Guidance for Industry

Handling and Retention of BA and BE Testing Samples

DRAFT GUIDANCE

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Handling and Retention of BA and BE Testing Samples

This draft guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to aid study sponsors and/or drug manufacturers, contract research organizations (CROs), site management organizations (SMOs), clinical investigators, and independent, third parties regarding the procedure for handling reserve samples from relevant bioavailability (BA) and bioequivalence (BE) studies, as required by §§ 320.38 and 320.63 (21 CFR 320.38 and 320.63). The guidance highlights (1) how the test article and reference standard for BA and BE studies should be distributed to the testing facilities, (2) how testing facilities should randomly select reserve samples, and (3) how the reserve samples should be retained. The guidance also clarifies and emphasizes points addressed in § 320.38.

II. BACKGROUND

Following the generic drug scandal in the 1980s, the FDA issued an interim rule on the retention of BA and BE testing reserve samples in the *Federal Register* of November 8, 1990.[2] The intent of the interim rule was to deter possible bias and fraud in BA and BE testing by study sponsors and/or drug manufacturers. Following public comments, a final rule was issued in the *Federal Register* on April 28, 1993.[3] Implementing regulations are located in 21 CFR 312.57(d), 314.125(b)(17), 314.127(b), 314.150(b)(9), 320.31(d)(1), 320.38, and 320.63.

In the preamble of the final rule, the Agency stated that the study sponsor and/or drug manufacturer should not separate out the reserve samples of the test article and reference

[1] This guidance has been prepared by the Division of Scientific Investigations in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] 55 FR 47034.

[3] 58 FR 25918.

standard before sending the drug product to the testing facility.[4] This is to ensure that the reserve samples are in fact representative of the batches provided by the study sponsor and/or drug manufacturer for the testing. The study sponsor and/or drug manufacturer should send to the testing facility batches of the test and reference products so that the testing facility can ***randomly select*** samples for testing, and material to maintain as reserve samples. The drug product should also be maintained in the sponsor's or manufacturer's original container (see section III).

In the preamble of the final rule, the Agency noted that reserve sample retention is the responsibility of the organization that conducts the BA or BE study.[5] The intent is to eliminate the possibility of sample substitution by the study sponsor and/or drug manufacturer, or prevent the alteration of any reserve samples from a study conducted by a contractor before release of drug product samples to the FDA.

FDA's Division of Scientific Investigations (DSI) and field investigators from the Office of Regulatory Affairs (ORA) conduct inspections of clinical and analytical sites that perform BA and BE studies for study sponsors and/or drug manufacturers seeking approval of generic and new drug products. A frequent finding from these inspections is the absence of reserve samples at the testing facilities where the studies are conducted. In many cases, DSI finds that testing facilities return reserve samples to the study sponsors and/or drug manufacturers, against the direction of the regulations as described in §§ 320.38 and 320.63. In other cases, study sponsors and/or drug manufacturers, SMOs, or contract packaging facilities designate the study test article and reference standard for each subject, and preclude the testing facilities from randomly selecting representative reserve samples from the supplies. DSI also finds that deviations from the regulations more often occur in BE studies with pharmacodynamic or clinical endpoints in which the studies are confused with clinical safety or efficacy studies. The pharmacodynamic or clinical endpoint studies are usually multisite, blinded studies conducted under contract (either directly with the study sponsor or drug manufacturer or via an SMO) by physicians or clinical investigators who use their own clinics or offices to conduct the studies. Moreover, some clinical investigators believe that they are not CROs and are not required to retain reserve samples. This guidance will clarify the responsibilities for retention of samples.

III. SAMPLING TECHNIQUES AND RETENTION FOR MULTIPLE STUDIES AND SHIPMENTS

The study sponsor and/or drug manufacturer should provide to the testing facility batches of the product to be tested and of the reference standard such that the reserve samples can be ***randomly selected***. This will ensure that these samples are in fact representative of the batches provided by the study sponsor and/or drug manufacturer and that they are retained in the study sponsor's original container. Because the study sponsor and/or drug manufacturer may provide a testing facility with a variety of container sizes and packaging, FDA is flexible in applying the

[4] 58 FR 25918 at 25920.

[5] 58 FR 25918 at 25921.

representativeness requirement as described in § 320.38. For example, the following random sampling techniques should be used by the testing facility for the container size and packaging described.[6] (The following text has been excerpted from the preamble of the final rule; bolded text is particularly relevant.)

Single Container – If a single container of the test article and of the reference standard are provided to the testing facility, the testing facility should remove a quantity of the test article and of the reference standard from their respective containers sufficient to conduct the study; the remainder of each container should be retained as reserve samples in the original containers.

Multiple Containers – If multiple containers of the test article and of the reference standard are provided to the testing facility, the testing facility should ***randomly select*** enough containers of the test article and of the reference standard to conduct the study; the remaining containers of the test article and reference standard should be retained as the reserve sample in the original containers.

Unit Dose – If the test article and reference standard are provided to the testing facility in unit dose packaging, the testing facility should ***randomly select*** a quantity of unit doses of the test article and of the reference standard sufficient to conduct the study; the remaining unit doses of the test article and of the reference standard should be retained as the reserve samples in the original unit dose packaging. ***It would not be appropriate to provide the test article and reference standard in unit dose packaging for the study and in bulk containers for the reserve samples because this would prevent the testing facility from randomly selecting the reserve samples.***

Blinded Study – If the study is to be blinded and the test article and reference standard are provided to the testing facility in unit dose packaging, with each unit dose labeled with a randomization code, ***the study sponsor and/or drug manufacturer should provide the testing facility with a labeled set of the test article and reference standard sufficient to conduct the study and with additional, identically labeled sets sufficient to retain the "five times quantity." The testing facility should randomly select a labeled set to conduct the study; the remaining labeled sets would be retained in their unit dose packaging as the reserve samples.*** For a blinded study, the study sponsor and/or drug manufacturer should also provide to the testing facility a sealed code for use by FDA should it be necessary to break the code (the sealed code should be maintained at the testing facility).

Retention for Multiple Studies and Shipments – If the same batches of the test articles and reference standard initially provided to the testing facility are used in performing more than one study, only one reserve sample of the test article and reference standard in sufficient quantity should be retained. The reserve samples should be identified as having come from the same batches as used in each study. However, if additional supplies of the test article and reference standard will be used by a testing facility to perform additional studies, the testing facility should retain a sufficient quantity of reserve samples from the subsequent shipment, regardless of

[6] 58 FR 25918 at 25920.

whether the shipment is from the same batch as that previously provided to the testing facility. This is to ensure that the reserve samples are in fact representative of the batch provided by the study sponsor and/or drug manufacturer to the testing facility.

IV. RESPONSIBILITIES IN VARIOUS STUDY SETTINGS

Because of the variety of study settings potentially involved in conducting BA and BE studies, several examples are provided here. These examples are not the only possible study settings. However, in ***all*** instances, the chain of custody of the retention samples used in the study should be preserved. The sponsor and/or manufacturer and any storage facility should document and maintain the transfer records for Agency verification.

A. Studies Conducted at CROs, Universities, Hospitals, or Physicians' Offices

CROs are the most common study site. Many BA/BE studies of oral dosage forms are conducted at CROs to support approval of abbreviated new drug applications (ANDAs), new drug applications (NDAs), and NDA supplements. CROs typically conduct single-site, open-label, crossover design studies with healthy volunteers as participants.

Study sponsors and drug manufacturers sometimes conduct BA and BE studies through university faculty, hospitals, or clinical investigators in private practice. The testing facilities are usually clinical study units in universities, hospitals, or clinics run by physicians.

The responsibilities of the study sponsor and/or drug manufacturer include:

1. Packaging, distributing, and shipping of the test article and reference standard to the testing facility
2. Monitoring of the study if it is conducted under an IND (rarely needed for most ANDA studies)

The responsibilities of the testing facility are as follows:

1. The clinical investigator or designee (such as the study coordinator or research pharmacist of the testing facility) should randomly select reserve samples from the supplies of test article and reference standard received from the study sponsor and/or drug manufacturer.
2. Reserve samples should be retained at the testing facility or at the pharmacy of the testing facility.
3. If the testing facility does not have an adequate storage facility, or goes out of business, the reserve samples can be transferred to an independent, third party with an adequate facility for storage under conditions consistent with product labeling.

Note: When studies are conducted at universities, hospitals, or physicians' offices, the clinical investigator or physician conducting the study should ***not*** send the reserve samples back to the study sponsor and/or drug manufacturer. The goal is to eliminate the possibility for sample

substitution by the study sponsor and/or drug manufacturer, or to preclude the alteration of a reserve sample from a study conducted by another entity before the release of the reserve sample to the FDA.

B. Studies Involving SMOs

When BA or BE studies are conducted by an SMO, they are frequently multisite, open-label studies of oral dosage forms in patients, or multisite, open-label studies of nonoral dosage forms with pharmacodynamic or clinical endpoints. Often, the study sponsor and/or drug manufacturer contracts with an SMO to recruit clinical investigators and to monitor a study. The SMO is involved directly or indirectly (i.e., by subcontracting to another party) in packaging and shipping of study test articles and reference standards to the testing facilities. The testing facilities are usually the clinical study units of CROs, universities, hospitals, or clinics run by physicians.

The responsibility of the study sponsor or drug manufacturer is to ship the test article and reference standard to the SMO under contract, or to the packaging facility under subcontract to the SMO.

The responsibilities of the SMO include:

1. Packaging, distributing, and shipping of test article and reference standard to all testing facilities (or subcontract a packaging facility to perform this function)
2. Monitoring of the study at different sites if it is conducted under an IND (rarely needed for most ANDA studies)

The SMO should ***not*** select and retain reserve study samples. As explained in the preamble of the final rule, the Agency intended that the selection of reserve samples for the study be performed at each testing facility.[7] However, following the completion of the study, if one or more of the testing facilities do not have an adequate storage facility, reserve samples can be transferred back to the SMO for storage.

The responsibilities of the testing facilities are as follows:

1. The clinical investigator or designee (such as the study coordinator or the research pharmacist of each testing facility) should randomly select reserve samples from the supplies of test article and reference standard received from the SMO under contract, or from the packaging facility under subcontract with the SMO.
2. Each testing facility or the pharmacy of each testing facility should retain the reserve samples.
3. If one or more of the testing facilities do not have an adequate storage facility, or go out of business, the reserve samples can be forwarded to an independent, third party with an adequate facility for storage under conditions consistent with product labeling. As stated

[7] 58 FR 25918 at 25920.

in subsection IV.A. above, the reserve samples should ***not*** be shipped back to the sponsor or manufacturer.

C. Blinded Studies With Pharmacodynamic or Clinical Endpoints Involving an SMO

Blinded BE studies are usually multisite and involve nonoral dosage forms with pharmacodynamic or clinical endpoints. Often, the study sponsor and/or drug manufacturer contracts with an SMO to recruit clinical investigators and to monitor the study. The SMO is involved directly or indirectly (i.e., by subcontracting to another party) in packaging and shipping of study test articles and reference standards to the testing facilities. The testing facilities are usually the clinical study units of CROs, universities, hospitals, or clinics run by physicians.

The responsibility of the study sponsor and/or drug manufacturer is to ship the test article and reference standard to the SMO under contract, or to the packaging facility under subcontract to the SMO.

The responsibilities of the SMO include:

1. Packaging, distributing, and shipping of test article and reference standard to all testing facilities (or subcontract a packaging facility to perform this function)
2. Monitoring of the study at different sites if it is conducted under an IND (rarely needed for most ANDA studies)

The SMO should not select and retain reserve study samples before study initiation (see previous example in subsection IV.B. for details).

The responsibilities of the testing facilities are as follows:

1. The clinical investigator or designee (such as the study coordinator or the research pharmacist of each testing facility) should randomly select reserve samples from the supplies of test article and reference standard received from the SMO under contract, or from the packaging facility under subcontract with the SMO. The clinical investigator should be aware of the sampling techniques used for blinded studies as described in section III.
2. Each testing facility or the pharmacy of each testing facility should retain the reserve samples. The sealed treatment code of the study should be kept at the testing facility.
3. If one or more of the testing facilities do not have an adequate storage facility, or go out of business, the reserve samples can be forwarded to an independent, third party with an adequate facility for storage under conditions consistent with product labeling.

D. Studies Conducted *In-House* by a Study Sponsor and/or Drug Manufacturer

It is uncommon for study sponsors and/or drug manufacturers to conduct BA/BE studies in their own facility. However, if a study sponsor and/or drug manufacturer does conduct such a study,

the same standards apply regarding the retention of study samples. The in-house clinical research unit should operate as an independent unit for the purposes of sample retention. All matters (e.g., manufacturing, purchasing, packaging, transfer records) concerning the test article and reference standard should be clearly documented and available to FDA investigators during an inspection. Standard procedures concerning security and accountability of the test article and reference standard for each study should be established to eliminate the possibility of sample substitution. To preclude any potential appearance of possible substitution, it would be prudent for study sponsors and/or drug manufacturers to remove themselves from reserve sample selection and retention. It is recommended that the firm engage a third party for retention of reserve samples.

The responsibility of the study sponsor and/or drug manufacturer (clinical research department) is to arrange packaging and transferring of the test article and reference standard to the in-house clinical study unit.

The responsibilities of the testing facility (in-house clinical study unit) are as follows:

1. All matters concerning the transfer and receipt of the test article and reference standard should be documented.
2. The clinical investigator, study coordinator, or research pharmacist (if available) in the clinical study unit should randomly select reserve samples from the supplies of test article and reference standard. It is recommended that an independent, third party be available to witness dosing and random selection of reserve samples.
3. Reserve samples should be retained in a secure room in the clinical study unit. To protect the study sponsor or drug manufacturer from challenge to the authenticity of the reserve samples, access to the room where samples are stored should be limited to the clinical investigator or research pharmacist. An entry log to the storage room should also be maintained. It is advised that an independent, third party be used for retention of reserve samples.

E. In Vitro BE Studies

Section 320.63 states:

> The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application.

Thus, the regulations for reserve samples apply to in vitro BE studies. The in vitro BE studies required for approval of nasal aerosols and nasal sprays for local action are an example of this. For an in vitro BE study, the roles of the study sponsor and/or drug manufacturer and the testing facility are similar to those described for in vivo BE studies conducted by CROs and in the examples of in vivo BE studies conducted in-house by a study sponsor and/or drug manufacturer.

V. EXCEPTION FOR INHALANT PRODUCTS

As stated in § 320.38(c), each reserve sample shall consist of a sufficient quantity of samples to permit FDA to perform five times all of the release tests required in the application or supplemental application. Dose content uniformity or spray content uniformity release tests alone usually take 30 units (canisters or bottles) per batch. Performance of other release tests may call for additional units. The number of reserve sample units that should be retained for three batches of test and reference product could exceed 1000 units (up to 250 units for each batch of the test and reference product) based on the "five times quantity" requirement. The Agency has determined that in lieu of the "five times quantity" requirement, the quantity of inhalant (nasal aerosol or nasal spray) test and reference standard retained for testing and analyses should be at least 50 units for each batch (see the preamble to the final rule).[8]

For ANDAs, at least 50 units of each of 3 batches should be retained for each of the test and reference products used in in vitro BE studies. One of these three batches is used in the in vivo study. If the in vivo or in vitro studies include placebo aerosols or sprays, at least 50 units of each placebo batch should also be retained. These recommendations apply only to nasal aerosol and nasal sprays for local action that are to be marketed as multiple dose products, typically labeled to deliver 30 or more actuations per canister or bottle.

[8] 58 FR 25918 at 25924.

GLOSSARY

Clinical Investigator – An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject) (21 CFR 312.3(b))

In this guidance, when a clinical investigation involves BA or BE studies, the clinical investigator has the responsibility of retaining the reserve samples at the testing facility or through an independent, third party.

Contract Research Organization (CRO) – A person that assumes, as an independent contractor with the sponsor or manufacturer, one or more of the obligations of a sponsor (e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA) (21 CFR 312.3(b))

This guidance addresses BA and BE studies submitted to support approvals of new and generic drugs. These studies are usually conducted by CROs under contract to study sponsors and/or drug manufacturers. Many CROs have their own testing facility, with physicians (to serve as clinical investigators) and clinical support staff (e.g., nurses, medical technologists) to conduct the BA and BE studies.

Independent, Third Party – In this guidance, *independent, third party* indicates a person that has no affiliation other than as an independent contractor with the study sponsor and/or drug manufacturer.

Reference Standard – In this guidance, *reference standard* refers to the reference product used in a BE study. It is usually the innovator's product or a marketed product of the drug under investigation. For BA studies, the reference standard can be an oral solution of the drug under investigation.

Site Management Organization (SMO) – In this guidance, *site management organization* (SMO) refers to a CRO that manages clinical study sites on behalf of the sponsor and/or drug manufacturer. An SMO should be an independent, third party.

Sponsor-Investigator – An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual (21 CFR 312.3(b)).

Study Sponsor – A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator (21 CFR 312.3 (b)).

In this guidance, the term *study sponsor and/or drug manufacturer* is used in recognition of the fact that most study sponsors are pharmaceutical companies that manufacture the drugs under investigation.

Testing Facility – A *testing facility* is considered to be the entity performing the bioavailability or bioequivalence study. The testing facility can be a CRO, university, hospital, clinic of a clinical investigator or in-house clinical study unit of a study sponsor and/or drug manufacturer, where dosing and blood sampling are performed. In issuing the final rule, the Agency intended that randomly selected reserve samples should be kept at the testing facility.